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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

JIANG, SHAOJIA A

ART UNIT PAPER NUMBER

1617

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/601,756

Applicant(s)

SCHREIBER, ALAN D.

Examiner

Shaojia A. Jiang

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

This application is a continuation of 09/658,867 now patented 6,610,674 which claims priority from Provisional Applications 60/156,434.

Applicant's preliminary amendment, submitted November 23, 2003 is acknowledged, wherein claims 1-11 are cancelled and claims 12-19 are newly submitted.

Currently, claims 12-19 are pending in this application.

Claims 12-19 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-19 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for progesterone, the particular esters of progesterone such as valerate, caproate esters of progesterone, or the particular progesterone analog, medroxyprogesterone acetate, employed for treating those inflammatory conditions recited in claim 12, does not reasonably provide enablement for all rest of progesterone analogs in claim 12 used in the claimed method of treating inflammatory conditions such as inflammatory bowel diseases.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention

is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of treating at least one of inflammatory conditions herein.

The state of the prior art: The skilled artisan would view that all rest of progesterone analogs such as an acetophenone derivative of 16a, 17a-dihydroxyprogesterone, allylestrenol, chlormadinone acetate, cyproterone acetate, desogestrel, dimethisterone, dydrogesterone, estrenols, ethinylestrenol, ethlestrenol, ethynodiol diacetate, hydroxyprogesterone caproate, megestrol acetate, norethandrolone, norethynodrel norgestimate, 19-nodestosterone, capable of treating inflammatory bowel diseases, but **not** causing inflammatory bowel diseases in the patient, are in question, since some progesterone analogs are known to trigger inflammatory bowel diseases in the patient (will discussed more below).

The predictability of the art, and the breadth of the claims: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 18 indicates that the more

unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hanker teaches in "*Gastrointestinal Disease and Oral Contraception*" (PTO-892) that the low doses of estrogens and progestogens such as the instant progestogen analogs: desogestrel, cyproterone acetate (CPA), chlormadinone acetate, noretynodrel, ethynodiol, and norethisterone acetate used in oral contraceptive (OC) may give an etiologic role in the development on Crohn's disease, or increase risk of Crohn's disease, or cause inflammatory bowel diseases in the OC women. See Hanker's the left paragraph at page 2206. Note that the instant dose (500 mg-2 g) is much higher than the OC treatment in general.

Thus, it is highly unpredictable whether administering high dose of all rest of progesterone analogs herein (except progesterone, valerate, caproate esters of progesterone, or medroxyprogesterone acetate) is useful in treating inflammatory bowel diseases herein without triggering the same diseases, according to the teachings of Hanker.

Moreover, Hanker teaches that some instant particular progesterones (progestogens) such as norethisterone, desogestrel, CPA and chlormadinone acetate do not undergo enterohepatic circulation. Other instant particular progestogens, i.e., noretynodrel, etynodiol, lynestrenol and norethisterone acetate are metabolized to norethisterone. Desogestrel is converted to 3-ketodesogestrel and norgestimate to norgestrel-17-beta-acetate and levonorgestrel. Hence, these progesterone analogs do not share same or substantial similar physical, chemical, biological and physiological properties or activities when administering to a host such as a woman.

Therefore, the teachings of Hanker support that it is highly unpredictable that all rest of progesterone analogs herein (except progesterone, valerate, caproate esters of progesterone, or medroxyprogesterone acetate) are useful in treating inflammatory bowel diseases.

Further, one of skill in the art would clearly recognize that for example the structure of chlormadinone acetate (known its chemical name, 6-Chloro-6-dehydro-17.alpha.-hydroxyprogesterone, see CAS STN Registry for chlormadinone: the name and structure, registered number 1961-77-9) is different substantially from progesterone since chlormadinone acetate has a double bond at 6 position and a chloro at 6, and a hydroxyl at 17 whereas progesterone does not have these functional groups. Thus, chlormadinone acetate is not deemed to have same or substantial similar biological and physiological activities and properties as progesterone does.

The amount of direction or guidance presented and the presence or absence of working examples: Note that only a single progesterone analog, medroxyprogesterone acetate, was tested for the treatment herein (see Example 1-5 at page 20-28 of the specification). Thus, the evidence in the examples is **not** commensurate in **scope** with the claimed invention and does not demonstrate criticality of a claimed range of the agents in the claimed method. See MPEP § 716.02(d).

Therefore, the enabling evidence for progesterone or its particular esters or medroxyprogesterone acetate is not considered to represent all the rest of progesterone analogs herein having the same or substantially similar effects.

Thus, the specification fails to provide sufficient support of the broad use of all of agents encompassed by the claims for inflammatory diseases. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of all agents encompassed by the instant claims suitable to practice the claimed invention.

Therefore, in view of the Wands factor and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test all agents encompassed in the instant claims for treating inflammatory bowel diseases, without causing inflammatory bowel diseases in the patient, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation, "derivative" in claim 12 render these claims indefinite. The recitation, "derivative" of the compound are not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "derivative" of the compounds. One of ordinary skill in the art would clearly recognize that any significant structural variation to

a compound would be reasonably expected to alter its properties, e.g., physical, chemical, physiological effects and functions. Thus, it is unclear as to what "derivative" of compounds herein would be encompassed thereby.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peat (4,439,432, of record in the parent application), in view of Bundgaard, "Design of prodrugs", 1985, Elsevier, page 1 (PTO-892) and Schreiber (4,902,681, of record in the parent application).

Peat discloses that progesterone is useful in methods for the treatment of intestinal inflammation and bowel spasms (see col. 1 lines 49-54) and the progesterone composition can be administered transdermally, orally, and in suppository and pessary form (see the abstract) or injectable form (see col. 1 lines 23-24) or orally in an encapsulated dosage form (see col. 3, Example 3 lines 20-21).

The prior art does not expressly teach the employment of the particular progesterone esters, valerate, caproate esters of progesterone in a method of treating a patient suffering from at least one of inflammatory conditions herein, and the

administration of valerate, caproate esters of progesterone to the patient in an amount which may be about 500 mg to about 2 g daily in an enteric coated tablet for targeted delivery to an affected portion of the GI tract.

Bundgaard teaches that esters of actives are most common prodrugs since esters of actives containing hydroxyl and carboxyl groups (also known as hydroxyl group in an alcohol and carboxyl group in a carboxylic acid conjugated or esterified by an ester bond) are hydrolyzed within the body (in vivo) by cleaving the ester bond to regenerate the active drug substances (see the bottom paragraph at page 1).

Schreiber teaches the effective amounts of progesterone for treating autoimmune disease is about 1-90 mg/kg/day (see col.5 lines 11-12; claim 13). Since a standard person weight is 70 kg, the range of effective amounts of progesterone is 1 mg/kg X 70 kg = 70 mg to 90 mg/kg X 70 kg = 6300 mg or 6.3 g which overlap with the instant range of dose, about 500 mg to about 2g daily.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer valerate, caproate esters of progesterone to a patient once a day in the amount of about 500 mg to about 2 g in a method of treating a patient suffering from at least one of inflammatory conditions herein.

One having ordinary skill in the art would have been motivated to administer a progestogenic compound to administer valerate, caproate esters of progesterone to a patient once a day in the amount of about 500 mg to about 2 g in a method of treating a patient suffering from at least one of inflammatory conditions herein because

Art Unit: 1617

progesterone is known to be useful in the treatment of inflammatory conditions herein such as intestinal inflammation and bowel spasms according the prior art.

Moreover, valerate, caproate esters of progesterone is considered to have same or substantial similar biological and physiological activities and properties and usefulness as progesterone does, since esters of progesterone having two moieties, progesterone and valerate or caproate, would be hydrolyzed within the body (in vivo) by cleaving the ester bond to regenerate the active drug, progesterone, in the body, based on the well known teachings of esters as prodrugs in pharmaceutical art according to Bundgaard.

Therefore, one of ordinary skill in the art would have reasonably expected that valerate, caproate esters of progesterone would have same usefulness as progesterone in a method of treating a patient suffering from at least one of inflammatory conditions herein. Moreover, daily oral administration of progesterone acetate is well known in the art.

Therefore, one of ordinary skill in the art would have been motivated to optimize the effective amount of valerate, caproate esters of progesterone to be administered to a patient once a day in the amount of about 500 mg to about 2 g since the optimization of amounts of known active agents and known dosage regimen to be administered is considered well within the skill of artisan.

Additionally, the usefulness of a similar encapsulated dosage form for oral delivery of progesterone in the treatment of disorders herein is also taught by Peat.

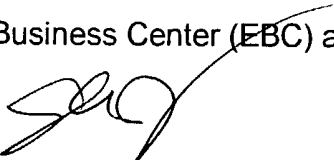
Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
September 1, 2004
